REMARKS

Amendments to the Claims

Claims 48, 50, 53-55, 57-62, 69, 70, 73 and 75 are pending. The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 48, 50, 57, 58 and 75 were amended and Claim 61 was canceled.

Support for Claims 48 and 50 can be found at, *e.g.*, pg. 12, line 7 through pg. 13, line 14; pg. 14, line 24 through pg. 15, line 2; and original Claim 61.

Support for Claims 57 and 58 can be found at, *e.g.*, pg. 76, line 11 through pg. 77, line 10; pg. 99, lines 8-14; Table 1; and FIG 3A.

Support for Claim 75 can be found at, *e.g.*, pg. 4, lines 17-19 and pg. 18, lines 10-11.

Claim Objections

The Examiner has objected to Claim 75 for failing to provide proper antecedent basis pursuant to 37 C.F.R. § 1.75(d)(1) on the ground that the specification refers to "N-acetyl-CRATKML-carboxamide" and Claim 75 recites "N-acetyl-CRATML-carcoximide."

The Applicants have amended Claim 75 to recite "N-acetyl-CRATKML-carboxamide" and respectfully request withdrawal of the objection to Claim 75.

Rejection Pursuant to 35 U.S.C. § 112, ¶ 1 Written Description

N-acetyl-CRATML-carcoximide

The Examiner has rejected Claim 75 as allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, ¶ 1. Specifically, the Examiner contends

that the specification fails to describe the inhibitor N-acetyl-CRATML-carcoximide. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

Amended Claim 75 recites "N-acetyl-CRATKML-carboxamide." Support for N-acetyl-CRATKML- carboxamide can be found at, *e.g.*, pg. 4, lines 17-19 and pg. 18, lines 10-11. As such, Claim 75 is described in full compliance with the written description requirement under 35 U.S.C. § 112, ¶ 1. Thus, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 1 written description rejection against Claim 75.

Structural limitations of SNAP-25.

The Examiner has rejected Claims 48, 50, 53-55, 57-62, 69, 70, 73, and 75 as allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, ¶ 1. Specifically, the Examiner contends that the specification fails to teach any structural limitations of SNAP-25. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

According to *MPEP* § 2163.02, the test of written description is whether the specification reasonable conveys to a person of ordinary skill in the art that the applicant was in possession of the claimed invention at the time of filing. Possession may be shown in a variety of ways, including, *e.g.*, by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

The Applicants submit that the specification teaches numerous structural limitations of SNAP-25 that result in a toxin-resistant SNAP-25 and/or toxin-inhibitory SNAP-25.

With respect to toxin-resistant SNAP-25s, the specification teaches that alterations of the P1 and/or P1' residues of a botulinum cleavage site in SNAP-25 produces a toxin-resistant SNAP-25. For example, the specification teaches that that alterations of the P1 and/or P'1 positions of a botulinum cleavage site in SNAP-25 produces a toxin-resistant SNAP-25 and discloses at least 15 single-substitutions that produce a toxin-resistant SNAP-25 molecules and over 36 multiple substitutions that produce a toxin-resistant SNAP-25 molecules. See,

e.g., pg. 13, line 25 through pg. 14, line 8; pg. 15, lines 14-29; pg. 22, line 14 through pg. 23, line 8; and Examples 1 and 2. As one instance, FIG. 3 of present specification teaches that changing the endogenous QR amino acids comprising the P1-P'1 positions flanking the cleavage bond of botulinum toxin A to QT, QA, AA, AK, KH, or WW result in a toxin-resistant SNAP-25. As another instance, the present specification teaches that changing the R located at the P1 position flanking the cleavage bond of botulinum toxin C1 to A, S, T, D or E produces a toxin-resistant SNAP-25. As yet another instance, the present specification teaches that changing the I located at the P'1 position flanking the cleavage bond of botulinum toxin E to F, G, S or N produces a toxin-resistant SNAP-25. Additionally, the present specification teaches that changing the RQIDRIM sequence comprising the cleavage site for botulinum toxin E to PQIKRIT results in a toxin-resistant SNAP-25. Lastly, based on the teaches of the present specification, a person of ordinary skill in the art would reasonably expect that insertions which disrupt the P1-P'1 cleavage sites would result in a toxin-resistant SNAP-25.

As another example, the specification also teaches that deletion of residues produces a toxin-resistant SNAP-25. As one instance, the present specification indicates that amino-terminal deletion of residues 202-206 of SNAP-25 creates a toxin-resistant SNAP-25. See, *e.g.*, pg. 17, lines 19-26; and Examples 1 and 2. As another instance, the present specification indicates that amino-terminal deletion of residues 1-141 of SNAP-25 creates a toxin-resistant SNAP-25. See, *e.g.*, pg. 20, lines 8-18; and Examples 1 and 2. A person of ordinary skill in the art would reasonably expect that similar deletions, such as, *e.g.*, deletion of amino acids 1-140, 1-139, 1-138, 1-137, 1-136, 1-135, 1-134, 1-133, 1-132, 1-131, 1-130, etc., would behave similarly the toxin-resistant SNAP-25 having amino acids 1-141 deleted. The present specification also discloses that combining the amino-terminal and carboxyl-terminal deletions will also produce toxin-resistant SNAP-25s. See, *e.g.*, pg. 20, lines 8-18; and Examples 1 and 2.

With respect to toxin-inhibitory SNAP-25, the specification teaches that alterations of the P1 and/or P1' residues of a botulinum cleavage site in SNAP-25 produces a toxin-inhibitory SNAP-25 and discloses many examples. See, *e.g.*, pg. 18, line 21 through pg. 19, line 4; pg. 29, line 19 through pg. 30, line 28; pg. 37, lines 6-28; and Example 1. As such, the

substitutions and insertions discussed above would also produce toxin-inhibitory SNAP-25s. In addition, the present specification indicates other alterations also produce a toxin-inhibitory SNAP-25. For instance, substituting the Q197 with C results in a toxin-inhibitory SNAP-25.

As another example, the specification also discloses many deletion-based alterations in SNAP-25 that produce a toxin-inhibitory SNAP-25. See, *e.g.*, pg. 29, line 19 through pg. 30, line 28; pg. 35, lines 22-25; pg. 38, lines 5-12; and Examples 1 and 2. As one instance, the present specification indicates that amino-terminal deletion of residues 198-206 of SNAP-25 creates a toxin-inhibitory SNAP-25. See pg. 29, lines 27-29. As another instance, the present specification indicates that amino-terminal deletion of residues1-180 or 1-186 of SNAP-25 creates a toxin-inhibitory SNAP-25. See pg. 30, lines 18-28. A person of ordinary skill in the art would reasonably expect that similar deletions, such as, *e.g.*, deletion of amino acids 1-181, 1-182, 1-183, 1-184, or 1-185, would behave similarly the toxin-inhibitory SNAP-25 having amino acids 1-180 or 1-186 deleted. The present specification also discloses that combining the amino-terminal and carboxyl-terminal deletions will also produce toxin-inhibitory SNAP-25s.

The specification further teaches how to generate and test for additional SNAP-25 variants useful as a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25. See, *e.g.*, pg. 23, lines 23-27 disclosing exocytosis assays; pg. 33, lines 5-8 disclosing treatment effect assays; pg. 33, line 18 through pg. 34, line 28 disclosing peptide synthesis techniques; pg. 38, lines 25-29 disclosing mutagenesis techniques; pg. 38, line 14 through pg. 45, line 14 disclosing DNA cloning and protein expression techniques. In addition, Examples 1 and 2 of the present specification illustrate how to use these disclosed techniques to generate and test for SNAP-25 variants useful as a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25.

Thus, the Applicants submit that the multitude of structural limitations, in the form of amino acid substitutions, deletions and insertions, taught by the present specification to be useful in creating a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 reasonable conveys to a person of ordinary skill in the art that the Applicants were in possession of the presently claimed methods at the time of filing. This is because the structural limitations taught are

distinguishing identifying characteristics of a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 sufficient to show that the Applicants were in possession of the claimed methods. Therefore, the Applicants submit that the present specification provides adequate written description support for all claims and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 1 written description rejection against Claims 48, 50, 53-55, 57-62, 69, 70, 73, and 75.

Rejection Pursuant to 35 U.S.C. § 102(b) Anticipation

I. Anticipation rejections by Carroll.

The Examiner has rejected Claims 48, 50, 53-55, 57-62, 69 and 70 as allegedly being anticipated under 35 U.S.C. § 102(b) by Sean B. Carroll et al., *Therapy for Clostridial Botulinum Toxin*, U.S. Patent 5,599,539 (Feb. 4, 1997), hereafter the "Carroll patent." As a basis for the anticipation rejections presently raised against the pending claims, the Examiner argues that the specification teaches that the term "SNAP-25" means any protein and cites the present specification at pg. 19, lines 15-27. See, April 10, 2007 Office Action at pg. 5, ¶ 4, lines 5-6. The Examiner contends that the Carroll patent anticipates on the ground that the disclosure inherently teaches the presently claimed methods "because SNAP-25 is a variant as described in the specification with insertions, deletions and substitutions and would also inherently be capable of performing substantially the equivalent function of a SNAP-25 in the absence of evidenced to the contrary." See, April 10, 2007 Office Action at pg. 6, ¶ 2, lines 11-14. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

First, the Applicants respectfully disagree with the Examiner's interpretation of the meaning for the term "SNAP-25." As pointed out by the Examiner, a polypeptide variant includes insertions, deletions, conservative substitutions and/or non-conservative substitutions. See present specification at pg. 19, lines 16-18. However, in the preceding paragraph, the specification indicates that a "toxin-resistant SNARE or toxin-inhibitory SNARE may be a variant, fragment, derivative or fusion of a naturally occurring SNARE with the required or preferred properties as set out above." See present specification at pg. 19, lines 12-14. As such, a toxin-resistant SNARE derived from a variant sequence of a naturally occurring

SNARE or a toxin-inhibitory SNARE derived from a variant sequence of a naturally occurring SNARE must possess required or preferred properties as defined by the present specification. For example, one required property a toxin-resistant SNARE or a toxin-inhibitory SNARE is that these SNAREs must in fact be SNAREs. This requirement is self-evident from the plain meaning of the term "SNARE" as used in the present specification and by a person of ordinary skill in the art. As such, the Applicant's respectfully submit that the Examiners interpretation of the term "SNAP-25" to mean any protein, including non-SNARE proteins, is untenable.

Second, according to *MPEP* § 2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

The Carroll patent discloses methods of "treating humans and animals intoxicated with a bacterial toxin by oral administration of antitoxin raised against the toxin." See, col. 3, lines 27-29; and col. 4, lines 21-23. The Carroll patent indicates that a preferred toxin includes BoNT/A, BoNT/B, BoNT/C1, BoNT/D, BoNT/E, BoNT/F, and BoNT/G. See, col. 4, lines 45-47; and Table 1. The antitoxin antibodies are obtained through immunization of mammals or non-mammals using an antigen. See. col. 4, lines 26-36; and Example s 1 & 3. Thus, the Carroll patent discloses methods of treating poisoning by a clostridial toxin in a patient by administering anti-clostridial toxin antibodies to a patient in need thereof.

Amended Claims 48 and 50 are directed towards a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 "capable of performing substantially the equivalent function to a naturally-occurring SNAP-25." As such, the anti-clostridial neurotoxin antibodies disclosed in the Carroll patent do not anticipate presently claimed methods because anti-clostridial neurotoxin antibodies are incapable of performing substantially the equivalent function to a naturally-occurring SNAP-25

Thus, the Applicants respectfully submit that the Carroll patent does not teach a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 as presently claimed because the anti-clostridial neurotoxin antibodies disclosed in the Carroll patent are 1) not SNAP-25 molecules; and 2) are incapable of performing substantially the equivalent function to a

naturally-occurring SNAP-25. Therefore, the Applicants respectfully submit that this rejection is unsupported and request withdrawal of the 35 U.S.C. § 102(b) anticipation rejection for Claims 48, 50, 53-55, 57-62, 69 and 70.

II. Anticipation rejections by Siegel.

The Examiner has rejected Claims 48, 50, 53, 57-62, and 70 as allegedly being anticipated under 35 U.S.C. § 102(b) by Lynn S. Siegel, *Human Immune Response to Botulinum Pentavalent (ABCDE) Toxoid Determined by a Neutralization Test and by an Enzyme-Linked Immunosorbent Assay*, 26(11) J. Clin. Microbiol. 2351-2356 (1988), hereafter the "Siegel reference." As a basis for the anticipation rejection presently raised against the pending claims, the Examiner argues that the specification teaches that the term "SNAP-25" means any protein and cites the present specification at pg. 19, lines 15-27. See, April 10, 2007 Office Action at pg. 7, ¶ 1, lines 6-7. The Examiner contends that the Siegel reference anticipates on the ground that the disclosure inherently teaches the presently claimed methods "because SNAP-25 is a variant as described in the specification with insertions, deletions and substitutions and would also inherently be capable of performing substantially the equivalent function of a SNAP-25 in the absence of evidenced to the contrary." See, April 10, 2007 Office Action at pg. 7, ¶ 2, line 11 through pg. 8, ¶ 1, line 2. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Siegel reference discloses a study that "surveyed personnel immunized with the MDPH botulinum toxoid for neutralizing antibodies to type A and to type B botulinum toxins." See pg. 2351, col. 2, ¶ 3, lines 1-3. This reference indicates that the purpose of the study was "to determine the immune status of personnel receiving the toxoid and to evaluate the effectiveness of the current vaccine. See, pg. 2351, col. 2, ¶ 3, line 6 through pg. 2352, col. 1, ¶ 1, line 2. The presence of anti-BoNT/A and anti-BoNT/B neutralizing antibodies was determined an ELISA method. See, pg. 2352, col. 1, ¶ 1, lines 2-5; and pg. 2353, col. 1, ¶ 3, line 1 through pg. 2353, col. 2, ¶ 2, line 22. Thus, the Siegel reference discloses an ELISA-based assay for measuring the amount of anti-BoNT/A and anti-BoNT/B neutralizing antibodies in individuals vaccinated with an anti-botulinum toxoid antigen.

Amended Claim 48 is directed towards a method of treating poisoning by a Clostridial toxin in a patient by administering a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25. Amended Claim 50 is directed towards a method of preventing poisoning by a Clostridial toxin in a patient by a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25.

First, even if the Applicants accepted the Examiner's interpretation of the term SNAP-25 to mean any protein, the Siegel reference does not anticipate the presently claimed methods because the disclosed ELISA-based assay is neither a method of treating Clostridial toxin poisoning nor a method of preventing Clostridial toxin poisoning. As such, the ELISA-based assay disclosed in the Siegel reference does not anticipate presently claimed methods because measuring the amount of anti-BoNT/A and anti-BoNT/B neutralizing antibodies in individuals vaccinated with an anti-botulinum toxoid antigen neither treats nor prevents poisoning by a Clostridial toxin.

Second, the vaccination procedure outlined in the Siegel reference does not anticipate the toxin-resistant SNAP-25 or toxin-inhibitory SNAP-25 presently claimed. The antigen used to elicit the immune response in personnel was the botulinum pentavalent (ABCDA) toxoid. See, pg. 2352, col. 1, ¶ 2, lines 1-6. The botulinum pentavalent (ABCDA) toxoid vaccine was manufactured by culturing *C. botulinum* serotypes A-E to produce crude preparations of neurotoxins which were then purified and detoxified by formalin treatment. See, *e.g.*, Michael P. Byrne and Leonard A. Smith, *Development of Vaccines for Prevention of Botulism*, 82(9-10) Biochimie 955-966 (2000).

As discussed above, the term SNAP-25 does not mean any protein and amended Claims 48 and 50 are directed towards a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 "capable of performing substantially the equivalent function to a naturally-occurring SNAP-25." As such, the botulinum penatvalent (ABCDA) toxoid disclosed in the Siegel reference does not anticipate presently claimed methods because botulinum penatvalent (ABCDA) toxoid is incapable of performing substantially the equivalent function to a naturally-occurring SNAP-25.

Thus, the Applicants respectfully submit that the Siegel reference does not teach a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 as presently claimed because 1) the Siegel reference does not disclose a method to treat or prevent poisoning by a Clostridial toxin and 2) the botulinum penatvalent (ABCDA) toxoid disclosed in the Siegel reference is not a SNAP-25 molecule and is incapable of performing substantially the equivalent function to a naturally-occurring SNAP-25. Therefore, the Applicants respectfully submit that this rejection is unsupported and request withdrawal of the 35 U.S.C. § 102(b) anticipation rejection for Claims 48, 50, 53, 57-62, and 70.

III. Anticipation rejections by Roland.

The Examiner has rejected Claims 48, 53, 57-62, and 69 as allegedly being anticipated under 35 U.S.C. § 102(b) by Elke H. Roland et al., *Infant Botulism: A Rare Entity in Canada?*, 135(2) CMAJ 130-131 (1986), hereafter the "Roland reference." As a basis for the anticipation rejection presently raised against the pending claims, the Examiner argues that the specification teaches that the term "SNAP-25" means any protein and cites the present specification at pg. 19, lines 15-27. See, April 10, 2007 Office Action at pg. 8, ¶ 4, lines 5-6. The Examiner contends that the Roland reference anticipates on the ground that the disclosure inherently teaches the presently claimed methods "because SNAP-25 is a variant as described in the specification with insertions, deletions and substitutions and would also inherently be capable of performing substantially the equivalent function of a SNAP-25 in the absence of evidenced to the contrary." See, April 10, 2007 Office Action at pg. 9, ¶ 1, lines 11-14. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

The Roland reference discusses the case history of an infant diagnosed with botulism. Initially believing the infant had an infection, health care providers administered the patient ampicillin and gentamicin. See pg. 130, col. 1, ¶ 1, lines 3-7. However, 20 minutes after administering the antibiotics, the infant's condition worsen and assisted ventilation was required. See pg. 130, col. 1, ¶ 1, lines 7-9. Subsequently, examination of stool samples revealed the presence of BoNT/A bacteria and toxin and a diagnosis of infant botulism was made. See pg. 130, col. 2, ¶ 2, lines 1-7. The Roland reference indicated that the infant

slowly recovered over two months with supportive treatment. See pg. 130, col. 2, ¶ 2, lines 7-8.

First, as discussed above, amended Claims 48 and 50 are directed towards a method of treating or preventing poisoning by a Clostridial toxin in a patient in need thereof. The Roland reference does not anticipate the presently claimed methods because ampicillin was administered to treat an infection in a patient in need thereof and not Clostridial toxin in a patient in need thereof. In fact, the Roland reference indicates that administering the antibiotics worsen the patient's condition when it states"[t]reatment with aminoglycosides for suspected infection, as in our patient, may have worsen the clinical picture." See pg. 130, col. 2, ¶ 4, line 1 through pg. 131, col. 1, ¶ 1, line 2. As such, the method of treating an infection disclosed in the Roland reference does not anticipate presently claimed methods because treating a patient with ampicillin neither treats nor prevents poisoning by a Clostridial toxin.

Second, the use of ampicillin as disclosed in Roland reference does not anticipate the toxin-resistant SNAP-25 or toxin-inhibitory SNAP-25 presently claimed. Ampicillin is a β-Lactam antibiotic that functions as a bactericide by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. As discussed above, the term SNAP-25 does not mean any protein and amended Claims 48 and 50 are directed towards a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 "capable of performing substantially the equivalent function to a naturally-occurring SNAP-25." As such, ampicillin disclosed in the Roland reference does not anticipate presently claimed methods because ampicillin is incapable of performing substantially the equivalent function to a naturally-occurring SNAP-25.

Thus, the Applicants respectfully submit that the Roland reference does not teach a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 as presently claimed because 1) the Roland reference does not disclose a method to treat or prevent poisoning by a Clostridial toxin and 2) ampicillin is not a SNAP-25 molecule and is incapable of performing substantially the equivalent function to a naturally-occurring SNAP-25. Therefore, the Applicants respectfully submit that this rejection is unsupported and request withdrawal of the 35 U.S.C. § 102(b) anticipation rejection for Claims 48, 53, 57-62, and 69.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. The Examiner is invited to call the undersigned agent if there are any questions. Please use Deposit Account 01-0885 for the payment of any extension of time fees under 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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